Remarks

Claims 1-22 were pending in the subject application. By this Amendment, claims 1-22 have been cancelled and new claims 23-39 have been added. The undersigned avers that no new matter is introduced by this amendment. Accordingly, claims 23-39 are currently before the Examiner for consideration. Entry of the amendments presented herein and favorable consideration of the pending claims is respectfully requested.

The applicants and the applicants' representative wish to thank Examiner Teller and Examiner Tate for the courtesy of the telephonic interview conducted with the undersigned on March 23, 2004, regarding the rejections under 35 U.S.C. §112, first paragraph. The remarks and amendments set forth herein are consistent with the substance of the interview and are believed to address the outstanding issues as discussed during the interview.

As an initial matter, the applicants note that the Examiner did not provide the initialed Form PTO-1449 indicating that the references submitted in the Information Disclosure Statement (IDS) dated April 22, 2002 have been considered, as requested in the previous Amendment submitted by the applicants on October 17, 2003. Copies of the IDS, the references cited, and the return receipt postcard with the PTO date stamp are submitted herewith. The applicants respectfully request that the Examiner confirm that the references cited in the Information Disclosure Statement submitted April 22, 2002 have been considered and made of record in the subject application.

By this Amendment, the first page of the specification has been amended to include government support information.

Claims 1-19 are rejected under 35 U.S.C. §112, first paragraph, as non-enabled by the subject specification. The applicants respectfully submit that the claimed invention is fully enabled by the subject specification. However, by this Amendment, the applicants have cancelled claims 1-19 and added new claims 23-39, in order to lend further clarity to the claimed subject matter. Support for this Amendment, can be found, for example, at page 13, lines 4-31, page 14, lines 2-34, page 42, lines 20-32, page 44, lines 17-32, and page 45, lines 1-5, of the specification, and the claims as originally filed.

The applicants' remarks in the previous Amendment submitted on October 17, 2003, in response to the rejection under 35 U.S.C. §112, first paragraph, are incorporated herein by reference. The instant Office Action again cites the Dermer publication (1994) for the assertion that tumor cell lines do not mimic conditions in the human body. As discussed during the telephonic Examiner interview, in the Declaration under 37 C.F.R. §1.132 by Dr. William Dalton, which was submitted with the previous Amendment, Dr. Dalton states that the Examiner is taking the statement at page 2 of the subject specification out of its proper context, resulting in an overly broad generalization. Specifically, page 2, lines 20-21 of the specification states "It is also known that certain resistance mechanisms may only be functional *in vivo*, where tumor cells continue to interact with environmental factors such as extracellular matrix (ECM) and cellular counter-receptors" (emphasis added). The examples in the subject specification include cytotoxicity assays using human drug-sensitive myeloma cells (8226/S cells) and human drug-resistant myeloma cells (8226/LR5, L-phenylalanine-mustard-resistant cells; and 8226/DOX6, doxorubicin-resistant cells) that are adhered to fibronectin, a major component of ECM. As indicated at page 12, lines 3-6, and page 17, lines 6-10, of the specification, drug-sensitive cells of the human myeloma 8226 cell line express both VLA-4 ($\alpha_4\beta_1$) and VLA-5 ($\alpha_4\beta_1$) integrin fibronectin receptors, and the cells adhere to fibronectin through $\beta 1$ integrin reactions. Thus, "the *in vitro* conditions prepared in the cytotoxicity assays described in the application do mimic or approximate the *in vivo* conditions most relevant for determination of cell adhesion-mediated drug resistance." Dalton Declaration, page 2, section 2.

The applicants submit that the Dermer publication has little relevance regarding the issue of enablement of the claimed invention. Dr. Dalton notes

the Dermer publication, which asserts that tumor cell lines do not mimic conditions in the human, is an editorial-style article as demonstrated by both the journal's disclaimer at the left of the page and the statements contained therein. For example, Dermer asserts that data from tumor cell lines 'cannot be relevant to cancer initiation in humans.' The enormous amount of research that continues to be carried out using tumor cell lines as cancer models contradicts Dermer's decade-old statement. Moreover, using statistical analysis and a survey of the clinical and pre-clinical literature, Voskoglou-Nomikos *et al.* (Voskoglou-Nomikos T. *et al.*, *Clin. Cancer Res.*, 9(11):4227-4239, 2003) recently verified that the *in vitro* human cell line model was predictive of Phase II clinical trial performance of cancer drugs. The relevance of the Dermer publication is also questionable because of what is not stated. For example, Dermer does not comment on the vast array of experimental conditions that can be applied to tumor cells to approximate the *in vivo* microenvironment, nor does

Dermer address the utility of tumor cell lines to evaluate potential modulators of the multi-drug resistance phenotype.

The applicants respectfully submit that there is a reasonable correlation between *in vitro* results obtained using multi-drug resistant tumor cell lines and modulation of drug resistance *in vivo*. The correlation of the drug resistance phenotype *in vitro* and *in vivo* is recognized in the art.

As discussed during the telephonic Examiner interview, the Salmon *et al.* publication (Salmon S. *et al.*, *Blood*, 78(1):44-50, 1991) and the Bellamy *et al.* (I) publication (Bellamy W., *et al.*, *Am. J. Pathol.*, 142(3):1993) were submitted with the previous Amendment for the Examiner's consideration. The Salmon *et al.* publication evaluates verapamil as a chemosensitizer for reversing multi-drug resistance in multiple myeloma both *in vitro* and in clinical trials. Verapamil was capable of sensitizing myeloma cells that exhibited resistance to doxorubicin and vincristine *in vitro*, and reversing multi-drug resistance in some patients with VAD-refractory myeloma. The Bellamy *et al.* publication describes an *in vivo* model of human multiple myeloma in the severe combined immunodeficient (SCID) mouse using both the RMI 8226 human myeloma cell line and P-glycoprotein-expressing multidrug-resistant 8226/C1N subline. Doxorubicin was effective in treating the drug-sensitive 8226 human-SCID xenografts. As Dr. Dalton indicates in his Declaration, "this study shows that the *in vitro* drug resistance phenotype was also observed in the *in vivo* model, indicating that the drug resistance phenotype characterized *in vitro* is preserved when the tumor cells are grown within an animal." The Bellamy *et al.* (II) publication (Bellamy W. *et al.*, *Adv. Clin. Chem.*, 31:1-61, 1994) was also submitted with the previous Amendment for the Examiner's consideration. Bellamy *et al.* (II) indicate at page 34, lines 30-35, that modulators of multi-drug resistance, such as verapamil, quinidine, and cyclosporine A and its analogs, retain their activity in animal models.

At page 3 of the instant Office Action, it is indicated that the Voskoglou-Nomikos *et al.* publication relates to non-small cell lung cancer under the disease-oriented approach, breast and ovarian cancers under the compound-oriented approach, and all four tumor types together, but does not mention myeloma or multiple myeloma. The applicants respectfully submit that the Dermer publication should not be accorded more probative value than the Salmon *et al.* publication, the Bellamy *et al.* (I) publication, and the Bellamy *et al.* (II) publication, on the basis of the Dermer

publication's lack of specificity. On the contrary, the Salmon *et al.* publication, the Bellamy *et al.* (I) publication, and the Bellamy *et al.* (II) publication are more relevant to the correlation of the drug resistance phenotype *in vitro* and *in vivo*.

Also submitted with Dr. Dalton's Declaration, as Exhibit B, was data demonstrating that adhesion of patient myeloma cells to fibronectin does confer resistance to melphalan. As Dr. Dalton states in section 5, "these data show that the CAM-DR phenotype established with our *in vitro* cell lines is indeed operative in primary myeloma patient specimens."

The applicants respectfully submit that an application for patent is not required to show that a claimed method of treatment of a disease condition results in a cure of that disease condition, or even that clinical efficacy is achieved. The *in vitro* model described in the subject specification was an accepted model for multi-drug resistance at the filing date of the subject application, and continues to be so. The applicants respectfully submit that the subject specification enables the claimed invention. Accordingly, the applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph.

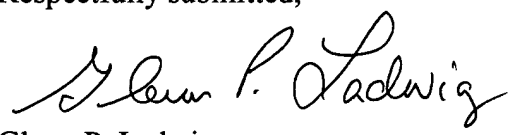
Claims 3, 5, 8, 10, 13, 15, and 20-22 are rejected under 35 U.S.C. §112, first paragraph, as lacking sufficient written description. The applicants respectfully submit that the subject specification provides a sufficient written description of claims 3, 5, 8, 10, 13, 15, and 20-22. The subject specification would convey to those of ordinary skill in the art that the applicants were in possession of the recited peptide, compositions, and methods at the time the application was filed. However, as indicated above, claims 3, 5, 8, 10, 13, 15, and 20-22 have been cancelled, rendering this rejection moot. New claims 23-39 have been added. Claims 23, 26, 29, 34, and 37 recite a peptide comprising the amino acid sequence of SEQ ID NO:6, or a pharmaceutically acceptable salt or variant thereof. Support for claims 23-39 can be found at page 13, lines 4-31, page 14, lines 2-34, page 42, lines 20-32, page 44, lines 17-32, and page 45, lines 1-5 of the specification, and the claims as originally filed. The applicants respectfully submit that one of ordinary skill in the art would appreciate that the applicants were in possession of the invention as currently claimed. Accordingly, the applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph.

In view of the foregoing remarks and amendments to the claims, the applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16 or 1.17 as required by this paper to Deposit Account 19-0065.

The applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



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Attachments: Copy of Information Disclosure Statement submitted April 22, 2002 with references
Copy of return receipt postcard for Information Disclosure Statement